

# World Journal of *Clinical Cases*

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## Therapy-related myeloid leukemia during erlotinib treatment in a non-small cell lung cancer patient: A case report

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### Abstract

#### BACKGROUND

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are tolerable drugs used for patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC). Serious adverse reactions are uncommon compared with cytotoxic drugs.

#### CASE SUMMARY

A 52-year-old man presented with general weakness and cytopenia. He had been taking erlotinib for 11 mo to treat NSCLC. The pathological diagnosis from the right upper lobe mass was adenocarcinoma with an EGFR mutation in exon 21 (L858R). He had previously received paclitaxel/carboplatin, gemcitabine/vinorelbine chemotherapy, stereotactic radiosurgery for brain metastasis, and whole-brain radiotherapy as treatment for NSCLC. We diagnosed the patient with acute myeloid leukemia (AML). During the induction and consolidation chemotherapy for AML, the erlotinib was discontinued. When complete remission of the AML was achieved, since the lung masses were increased, pemetrexed/cisplatin for the NSCLC was initiated. After two cycles of chemotherapy, the cytopenia was prolonged. AML relapse occurred with the same karyotype.

#### CONCLUSION

Therapy-related acute myeloid neoplasm (t-MN) is a rare but fatal late complication. Although a patient may be taking EGFR-TKIs, the possibility of t-MN should be considered. Further studies are needed to determine whether EGFR-TKI usage is a predisposing factor for t-MN.

**Key Words:** Acute myeloid leukemia; Erlotinib; Neoplasm, second primary; Non-small cell lung cancer; Case report

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**Core Tip:** Therapy-related acute myeloid leukemia (t-AML) developed during erlotinib treatment in a patient with epidermal growth factor receptor (EGFR)-mutant advanced non-small cell lung cancer (NSCLC). Alkylating cytotoxic drugs and radiotherapy are common treatments for patients with NSCLC. Cases of t-AML related to alkylating agents typically have a long latency period. Since it was 20 mo in this case, EGFR-tyrosine kinase inhibitor (EGFR-TKI) usage may be related to or hasten AML development in patients who previously received cytotoxic chemotherapy. Although the mechanism remains unclear, when a patient takes an EGFR-TKI, t-AML development should be considered, especially if cytopenia persists.

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## INTRODUCTION

Therapy-related acute myeloid leukemia (t-AML) is a rare but fatal late complication of cytotoxic chemotherapy. According to Surveillance, Epidemiology, and End Results data in United States cancer registries, 18 patients with t-AML were identified in 2001–2008 among 37008 non-small cell lung cancer (NSCLC) patients who received initial chemotherapy in adulthood[1]. Since patients with NSCLC receive multiple lines of treatment, it is difficult to determine which of the cytotoxic drugs are related to the AML that occurs several years later.

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the target therapy for patients with EGFR-mutant NSCLC. EGFR-TKIs are known to be relatively tolerable drugs for patients and less toxic than cytotoxic agents. Moreover, serious adverse reactions to them are uncommon[2].

We identified a case of AML that developed during erlotinib treatment and reviewed cases of myeloid neoplasms that occurred during EGFR-TKI treatment in the literature.

## CASE PRESENTATION

### Chief complaints

A 52-year-old man presented with general weakness. His symptoms had waxed and waned during the past several months.

### History of present illness

He was under lung cancer treatment consisting of erlotinib 100 mg/d, levetiracetam 1000 mg/d, and prednisolone 10 mg/d to control his symptoms and prevent seizure that related with brain metastasis.

### History of past illness

He had a medical history of chemotherapy and radiotherapy for NSCLC diagnosed as adenocarcinoma, T2bN2M1a by the International Association for the Study of Lung Cancer seventh edition guidelines 20 mo prior. The pathological diagnosis of the right upper lobe mass was adenocarcinoma with an EGFR mutation in exon 21(L858R). As first-line chemotherapy, he received six cycles of combination paclitaxel (175 mg/m<sup>2</sup>) and carboplatin (AUC 4). At that time, EGFR-TKI was not covered by medical insurance benefits as the first-line therapy, so cytotoxic chemotherapy was administered. After disease progression occurred, he received three cycles of gemcitabine (1000 mg/m<sup>2</sup>) and vinorelbine (25 mg/m<sup>2</sup>) chemotherapy. He then developed memory problems and gait difficulties. Brain magnetic resonance imaging revealed a brain metastasis. We decided to perform stereotactic radiosurgery using a Cyberknife to resect multiple metastatic lesions (total 23 Gy). Six months later, the size and number of brain metastatic lesions had increased. He subsequently received whole-brain

radiotherapy (total 30 cGy).

### **Personal and family history**

Our patient, who ran a flower shop, was a former smoker with a 26 pack-years history of smoking. He had quit smoking a year prior.

### **Physical examination**

His vital signs and physical examination findings were unremarkable except for a chronic ill-looking appearance.

### **Laboratory examinations**

A complete blood count revealed a white blood cell count of 7600 (absolute neutrophil count, 500), hemoglobin level of 12.4 g/dL, and platelet count of 83000/ $\mu$ L. A leukocyte differential count revealed an absolute neutrophil count of 500/ $\mu$ L, lymphocyte count of 2400/ $\mu$ L, and monocyte count of 1000/ $\mu$ L. Immature cells were observed in the peripheral blood (Figure 1A). The chemistry results were normal except for a lactate dehydrogenase level of 293 U/L (reference interval, 106–211 U/L).

### **Imaging examinations**

In the initial diagnosis, chest computed tomography revealed a 61 mm  $\times$  44 mm lobulated mass in the right upper lobe and another 31 mm  $\times$  23 mm spiculated mass in the left upper lobe. As the third-line therapy, we started erlotinib, an EGFR-TKI, at a dose of 150 mg/d 11 mo prior. During erlotinib treatment, the mass in the right upper lung became markedly improved (Figure 2A and B).

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## **FINAL DIAGNOSIS**

Bone marrow aspirate smears revealed a monocytic blast rate of 77.3% (Figure 1B). Eosinophil levels in the bone marrow were increased (14.4%). A bone marrow biopsy revealed 80% cellularity. While megakaryocytes were decreased, immature cells diffusely infiltrated the bone marrow. CBFB/MYH11 rearrangement was observed by fluorescence in situ hybridization analysis. On a chromosome analysis, inv(1) and inv(16) were detected. The patient's karyotype was 46, XY, inv(1) (p22q32), inv(16) (p13.1q22).

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## **TREATMENT**

After receiving the diagnosis of AML, the patient started induction chemotherapy with daunorubicin/cytarabine and consolidation chemotherapy with high-dose cytarabine. During AML treatment, the erlotinib treatment was stopped.

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## **OUTCOME AND FOLLOW-UP**

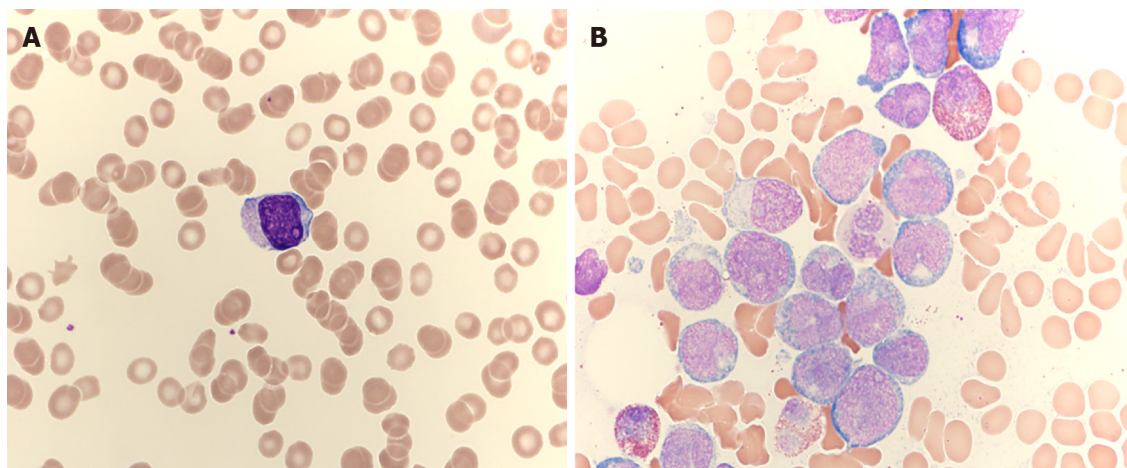
At the time that complete remission of the AML was achieved, both upper lobe masses had increased in size (Figure 2C and D). Fourth-line chemotherapy with pemetrexed/cisplatin for NSCLC was initiated. After two cycles of chemotherapy, the cytopenia persisted. The complete blood count revealed a white blood cell count of 1800 (absolute neutrophil count, 972), hemoglobin level of 9.6 g/dL, and platelet count of 88000/ $\mu$ L. Immature cells were observed in the peripheral blood. The result of the bone marrow study was AML relapse with the same karyotype. Re-induction chemotherapy with mitoxantrone/etoposide did not achieve remission. We administered low-dose cytarabine chemotherapy; the patient was exhausted with poor performance status and died of respiratory failure 10 mo after receiving the AML diagnosis.

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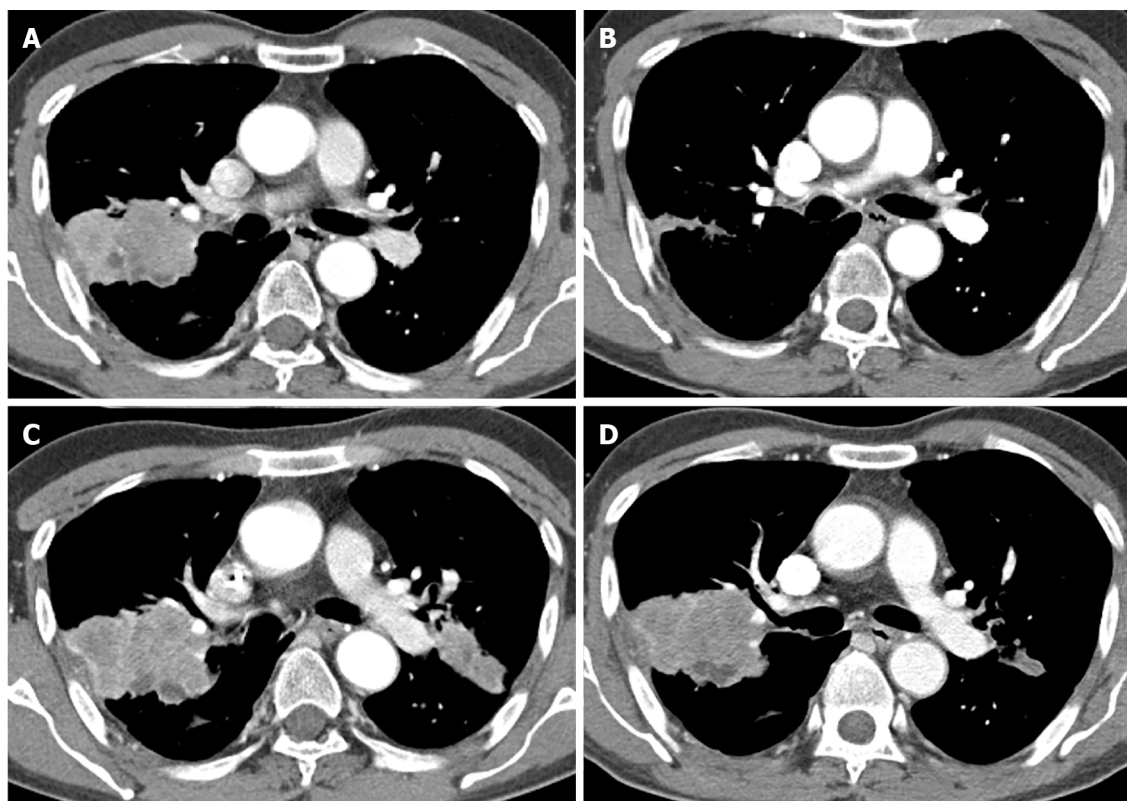
## **DISCUSSION**

This case involved t-AML that developed during erlotinib treatment in a patient with NSCLC. The case was considered a therapy-related myeloid neoplasm rather than de





**Figure 1 Blood smear and bone marrow aspiration results.** A: The blood smear shows 44% blast cells ( $\times 1000$ ); B: The bone marrow aspiration showed 77.3% myoblasts ( $\times 1000$ ).



**Figure 2 Contrast-enhanced chest computed tomography findings.** A: Before erlotinib treatment, a 59 mm  $\times$  42 mm heterogenous enhancing lobulated mass in the right upper lobe (RUL) is closely abutting the adjacent costal pleura with focal thickening and retraction; B: During erlotinib treatment, the mass in the RUL is markedly improved; C: Four months after discontinuing the erlotinib due to leukemia induction chemotherapy, the mass in the RUL is enlarged, and a spiculated mass is visible in the left upper lobe (LUL) (24 mm  $\times$  17 mm); D: Two months after pemetrexed/cisplatin treatment, no remarkable changes in the RUL and LUL masses are noted.

novo AML because the patient had a clinical history of antecedent cytotoxic therapy and radiotherapy. Carboplatin and radiotherapy in this patient were risk factors for t-AML[3]. Patients with t-AML related to alkylating agents generally experience a longer latency period (5–7 years) than those with t-AML related to topoiso-merase-2 inhibitors (2–3 years) between therapy and myeloid neoplasm development[4]. This can predict the long interval between alkylating chemotherapy and an AML diagnosis. However, in the present case, the interval between the initiation of carboplatin treatment and AML development was 20 mo, which was relatively short.



**Table 1 Literature review findings of therapy-related myeloid neoplasms after epidermal growth factor receptor tyrosine kinase inhibitor treatment in non-small cell lung cancer patients**

Patients number	Ref.	Age/sex	Pathological type of NSCLC	Initial stage	EGFR mutation	Prior chemotherapy	Interval from first line treatment	Prior radiotherapy	Duration of EGFR-TKI treatment	Interval from EGFR-TKI treatment until leukemia	CBC profiles at leukemia presentation: WBC (ANC) (μL)-hemoglobin (g/dL)/hematocrit (%)-platelets (mL)	Characteristics (Karyotype) of leukemia/MDS	Survival after diagnosis of leukemia
1	Uchida <i>et al</i> [8], 2005	49/M	Adenocarcinoma	IV (T1N0M1)	NA	Cisplatin/docetaxel/irinotecan 2 cycles	36 mo	Cyberknife for brain metastasis (22.993Gy)	Gefitinib, 15 mo	15 mo	NA	APL, normal karyotype, PML RARα positive	NA
2	Uchida <i>et al</i> [8], 2005	65/M	Squamous cell carcinoma	IIIB (T4N3M0)	NA	Cisplatin/mitomycin/vinorelbine 2 cycles, Uracil/tegafur for 2 mo in adjuvant setting	48 mo	Fractionated radiotherapy (2Gy* 25)	Gefitinib, 25 mo	25 mo	NA	APL, normal karyotype, PML RARα positive	NA
3	Uchida <i>et al</i> [8], 2005	72/M	Adenocarcinoma	IA (T1N0M0)	NA	Carboplatin/paclitaxel 1 cycle, Cisplatin, carboplatin, irinotecan, docetaxel, gemcitabine, vinorelbine, paclitaxel, amrubicin	69 mo	None	Gefitinib, 5 mo + 4 mo (discontinued and restarted)	26 mo	NA	APL, normal karyotype, PML RARα positive	NA
4	Ennishi <i>et al</i> [9], 2006	51/F	Adenocarcinoma	Recurrence after LLL lobectomy, mediastinal LN metastasis	NA	Carboplatin/paclitaxel 6 cycles	NA	Radiotherapy at a total dosage of 60 Gy	Gefitinib, 14 mo	14 mo	2300-13.2/-15200	APL, t(15;17)(q22;q21), PML/RARα positive	NA
5	Stathopoulos <i>et al</i> [6], 2010	67/M	Adenocarcinoma	IIIB	NA	Cisplatin/gemcitabine 6 cycles	11 mo	None	Erlotinib, 4 mo	8 mo	Grade 4 thrombocytopenia	MDS, 46, XY, del(20)(q11)[15]/47, idem, + 21(7)/48, idem, 21, + 21[-3]	NA
6	Stathopoulos <i>et al</i> [6], 2010	70/M	Adenocarcinoma	IIIB	NA-	Cisplatin/paclitaxel 6 cycles	12 mo	None	Erlotinib, 8 mo	8 mo	WBC 92000	CML, BCR-ABL+	NA
7	Stathopoulos <i>et al</i> [6], 2010	60/F	Adenocarcinoma	IIIB	NA	Cisplatin/vinorelbine 6 cycles. Carboplatin/etoposide 3 cycles	36 mo	Radiotherapy (RT) of the primary lung lesions and of the mediastinum	Erlotinib, 8.5 mo	8.5 mo	2500-/28.8-72000	MDS, RAEB-T/t-AML, 46, XX, del(7)(q22), add(21)(q22)	Died 3.5 mo later
8	Stathopoulos <i>et al</i> [6], 2010	59/F	Squamous cell carcinoma	IV	NA	Carboplatin/etoposide 6 cycles	14 mo		Erlotinib, 5.5 mo	5.5 mo	3200-/25.7	MDS, RAEB 47, XX, +8, t(5;9)(q13;q34)	Died 8 mo later

9	Moon <i>et al</i> [7], 2014	72/M	Squamous cell carcinoma	II (T2N1M0)	NA	A combination of radiotherapy and a repeated chemotherapy regimen (4 trials, 13 cycles) consisting of docetaxel, cisplatin, gemcitabine, vinorelbine, gefitinib, irinotecan, and carboplatin	10 yr	Combination of radiotherapy and a repeated chemotherapy regimen	Gefitinib, Duration:NA	NA	1700 (780)-5.2/-34000	T-AML (Acute megakaryoblastic leukemia)-5,-7,+2mar	Being followed up
10	Present case	52/M	Adenocarcinoma	IV (T2bN2M1a)	L858R	Paclitaxel/carboplatin 6 cycles, gemcitabin/ vinorelbine 3 cycles	20 mo	Cyberknife for brain metastasis (23Gy), WBRT (30Gy)	Erlotinib, 11 mo	11 mo	7600(500)-12.4/-83000	AML, 46, XY, inv(1)(p22q32), inv(16)(p13.1q22)	Died 10 mo later

APL: Acute promyelocytic leukemia; ANC: Absolute neutrophil count; CML: Chronic myeloid leukemia; EGFR: Epidermal growth factor receptor; EGFR-TKI: Epidermal growth factor receptor tyrosine kinase inhibitor; MDS: Myelodysplastic syndrome; NA: Not applicable; NSCLC: Non-small cell lung cancer; RAEB-T: Refractory anemia with excess blasts in transformation; t-AML: Therapy-related acute myeloid leukemia; WBC: White blood cell.

Differentiating therapy-related acute myeloid neoplasm (t-MN) from *de novo* myelodysplastic syndrome (MDS)/AML is difficult because mutation profiling has demonstrated similar abnormalities for both conditions. Common patterns in recurrent mutations and chromosomal abnormalities are chromosome 5 and 7 loss with alkylating agent exposure and *MLL* translocations at 11q23 or *RUNX1/AML1* at 21q22 with topoisomerase-2 inhibitor exposure[4,5]. However, *de novo* and therapy-related MDS/AML can share genetic features (especially the 11q23 anomaly). There are no pathognomonic morphologic or genetic features of t-MN[5].

EGFR-TKIs are the current first-line treatment for patients with EGFR mutation-positive advanced NSCLC. There have been a few reports related to leukemia and EGFR-TKIs[6-9]. In the literature review (Table 1), we identified eight patients with t-MN after EGFR-TKI treatment for antecedent NSCLC. The mean interval from the first-line NSCLC treatment to AML development was 40.7 (range, 11-120) months. None of the patients who were diagnosed with t-MN after EGFR-TKI treatment for NSCLC had taken topoisomerase II inhibitors. Since the latency period for these patients was not longer than expected, we considered the possibility that EGFR-TKI might be associated with the development of myeloid neoplasms.

The duration of EGFR-TKI therapy before AML was relatively short (mean, 13.4 mo; range, 5.5-26 mo). However, since cytotoxic chemotherapy drugs were administered prior to EGFR-TKI in all of these patients, the development of myeloid neoplasm may be related to both classes of drugs. It was not known whether the occurrence of t-MN was different depending on the type of EGFR mutation. This is because out of the 8 reported cases, only our case (L858R) provided the type of EGFR mutation.

Several case reports have shown that EGFR-TKIs might have leukemogenic effects in patients with t-MN after the administration of EGFR-TKIs[6,8,10]. However, after EGFR-TKIs were commercially approved, to the best of our knowledge, no cases of myeloid neoplasms after the administration of EGFR-TKI alone for NSCLC treatment have been reported in the literature. All patients of case reports with t-MN received

chemotherapy or radiotherapy for NSCLC treatment before receiving EGFR-TKIs. We suggest that EGFR-TKI may be related to or shorten the interval to AML development when patients previously received cytotoxic chemotherapy. According to the historical concept, cytotoxic drugs such as topoisomerase II inhibitors or radiotherapy induce DNA damage that leads to translocation. In the model for the role of clonal selection [4], clonal hematopoiesis of indeterminate potential (CHIP) is characterized by the absence of morphological evidence of disease and the presence of a clonal population of hematopoietic cells with somatic mutations in the genes associated with hematologic malignancies[11].

Toxins, drugs, oligoclonality with aging, chemoradiation, chemical exposure, immune destruction, or dysfunctional hematopoiesis may be selected for mutant clones and induce CHIP. Additional somatic alterations in CHIP can promote high-risk myeloid neoplasms. We considered the possibility that certain effects of EGFR-TKI on the tyrosine kinase pathway could play a role in CHIP.

Long-term epidemiological research is needed to clarify whether there is a relationship between EGFR-TKI treatment and the rare but serious events noted here. If the incidence of this complication in the EGFR-TKI-treated cohort is beyond that expected on the basis of patients with NSCLC before EGFR-TKIs are commercially available, we must consider EGFR-TKIs as the predisposing factor of t-MN.

## CONCLUSION

In summary, if cytopenia persists in patients treated with EGFR-TKIs for NSCLC, the possibility of t-MN should be considered. Further studies are needed to determine whether the administration of EGFR-TKIs is a predisposing factor for t-MN.

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